Remarks

Claims 1-11, 13, 14, 16-74, 76-83, 87, 89-92, 134, 135, 138, and 142 are pending. Claims 84-86 were inadvertently combined with claim 83 in the February 9, 2009 response, therefore we have corrected that in the above listed claims.

Applicants note that in the Office Action Summary under Disposition of Claims (4a), claim 13 is listed as withdrawn when, in fact, claim 13 is still pending. Under item (6), claim 14 is listed as rejected although this claim is not rejected, but rather objected to.

Rejections Under 35 U.S.C. § 112, first paragraph related to a CMV/Beta Actin fusion promoter

Claims 1, 4, 6, 16-18, 25 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection. The claims were also rejected under35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not enabled. While Applicants understand the standards for enablement and written description are separate under Federal Circuit case law, both the present enablement and written description rejections related to the CMV/Beta Actin fusion promoter are deficient in the same way. For this reason, and for ease of understanding, the rejections are discussed together, but should the need arise Applicants reserve the right to argue each rejection separately.

The Office Action states that the above mentioned claims are rejected based on reasons of record from the March 26, 2008 Office Action. The March 2008 Office Action states that "in the instant case, neither the art nor the specification teaches how to take regulatory regions of CMV and beta-actin and combine them to arrive at a functional, constitutive promoter." The current Office Action states that Daly et al. 2001 does not sufficiently overcome the rejection since Daly et al. allegedly teaches a construct comprising a hybrid promoter comprised of a CMV enhancer and a beta-actin promoter. Daly et al. allegedly does not teach, a hybrid of a CMV promoter and

a beta-actin promoter and therefore the claims lack sufficient written description. The present Office Action maintains the enablement rejection on this same basis.

In addressing this rejection, the Office Action provides no evidence indicating that the claimed constructs would not work as indicated. The specification clearly asserts, as discussed below, that the inventor was in possession of the said constructs and provides techniques and information for making and using the claimed constructs. Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements (*In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The Patent Office has not met this burden. The Office Action provides no evidence or convincing argument, as required, that the claimed compositions could not be made and used as described in the specification, let alone for the minimal information required for enablement (see discussion below). Thus, no proper *prima facie* case for lack of written description, or for enablement, has been established.

The rejection offers no support for, or explanation of, the conclusion that the skilled artisan would not have believed the applicant to be in possession of the claimed constructs (written description), nor that the constructs could not be made and used as described in the specification and understood by the skilled artisan (enablement). The Patent Office must accept the objective truth of the statements in the specification regarding the claimed compositions or must provide evidence or convincing reasoning to the contrary. This has not been done. Rather, the rejection merely states that the standard for rejection has been met without providing evidence or sound reasoning on which the conclusion could be fairly based[1]. Thus, the present rejection is improperly based on mere conjecture and assertion.

[1] Applicants acknowledge that the Examiner has reviewed the references provided in support, but maintain that the Examiner has merely asserted their lack of relevance for which they were submitted. This does not correct the lack of a prima facie case of non-enablement or lack of written description.

Further, there is no requirement that the claimed method be actually *demonstrated,*[2] either for written description purposes or for enablement purposes. Thus, the fact that the Applicants have not specifically made the claimed construct cannot serve as the sole basis of a rejection. For all of these reasons applicants submit that no proper *prima facie* case for lack of enablement has been established.

It is axiomatic that only that which is actually claimed need be enabled and described.[3] Thus, for the specification to teach how to make and use the claimed invention, all that is required is a discussion of the various parts of the claimed construct along with adequate information on how to make and use the claimed constructs.

Furthermore, the rejections, both the written description rejection and the enablement rejection provided by the Patent Office, only make reference to the components of claim 25, but the rejection is applied over claims 1, 4, 6, 16-18 which do not specifically recite the "offending" combination of a CMV/beta actin fusion promoter. There is a clear difference between a claim positively reciting an allegedly non-enabled step and a claim that *could* include a step that is alleged to be non-enabled. Assuming that the specific embodiment of claim 25 lacks enablement and/or written description, this does not necessarily mean that all claims that could encompass that embodiment, such as claims 1, 4, 6, 16-18 would also lack written description and be non-enabled. The current rejections for lack of enablement and written description violate this principle. Said another way, the possible inoperability of some embodiments which can be construed to be encompassed by a claim is not a bar to patentability. It is not a function of the

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[2]See *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987) (the mere fact that something has not previously been done is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it).

[3]see *Christianson v. Colt Industries Operating Corp.*, 822 F.2d 1544, 1565, 1 USPQ2d 1241, 1255 (Fed. Cir. 1987), *vacated, and remanded with instructions to transfer appeal to Court of Appeals for the Seventh Circuit*, 108 S. Ct. 2166, 7 USPQ2d 1109 (1988), *on remand*, 870 F.2d 1292, 1299, 10 USPQ2d 1352, 1357 (7th Cir. 1989) ("Because only the claimed invention receives patent law protection, the disclosures need generally be no greater than the claim.")("The 'invention' referred to in the enablement requirement of section 112 is the *claimed* invention") Furthermore, see *Amgen v. Hoechst*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) finding that it is clear that every detail of every embodiment is not required. For example, if subject matter is referred to in the specification as being part of the invention, and if that subject matter is not new or unknown subject matter that ordinarily skilled artisans would easily miscomprehend, then such subject matter is adequately described as required by 35 U.S.C. § 112, first paragraph. *Id.* at 1332.

claims to exclude every possible inoperable embodiment.[4] Applicants assert that even if the Examiner maintains the present rejections against claim 25, it is not necessary, nor even proper, to maintain the rejections against claims 1, 4, 6, 16-18.

The Office Action further rejects the other citations (Beattie et al., 2008, Klein et al., 2008, Nguyen et al., 2008, and Tenenbaum et al., 2004) due to the fact that "all these publications are after the time of filing and cannot be relied upon for support at the time of filing."

An important distinction has been made by the Courts between evidence of the knowledge and ability of those of skill in the art at the time of filing and evidence to prove that statements made in the application are correct. In the former case, of course, only evidence which existed prior to the filing of the application, or evidence that certain knowledge existed at the time of filing, is admissible (*In re Hogan*, 194 USPQ 527 (CCPA 1977)). In the latter case, any evidence, developed at any time is permissible and may be considered.

The Hogan Court also affirmed another principle that is relevant to the question of what evidence applicants may present. In correcting the Patent Office for applying a later state of the art to find an application non-enabling, the Court stated: "Courts should not treat the same legal question, enablement under § 112, in one manner with respect to the applicant and in a different manner with respect to the examiner." This confirms that the types of evidence that the Patent Office is permitted to use may also be used as evidence by applicants.

The clearest affirmation of the seasonability of factual evidence developed after the filing date of an application occurs in *In re Marzocchi* (169 USPQ 367, 370 (CCPA 1971)). In

[4]See *In re Anderson*, 471 F.2d 1237, 1242 (CCPA 1973), ("[I]t is always possible to put something into a combination to render it inoperative. It is not a function of the claims to *exclude* all such matters but to point out what the combination is."); *Ex parte Cole*, 223 USPQ 94, 95-96 (PTO Bd. App. 1983) ("Claims are addressed to the person of average skill in the particular art. Compliance with 112 must be adjudged from that perspective, not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art skilled would assuredly not choose such a combination."); *Horton v. Stevens*, 7 USPQ2d 1245, 1247 (Bd. Pat. App. & Int'f 1988) ("The mere fact that a claim embraces undisclosed or inoperative species or embodiments does not necessarily render it unduly broad."); and *Ex parte Breuer*, 1 USPQ2d 1906 at 1906 (Bd. Pat. App. & Int'f 1986) ("The issue is not whether the examiner can conjure up a substituent group...which does not exist. A person having ordinary skill in the art would readily appreciate that compounds containing such substituent group[s] do not exist....'[N]obody will use them...and the claims do not cover them'.")

discussing rejections under 35 USC § 112 where an examiner asserts that the unpredictability of the art creates a reasonable doubt as to the accuracy of a particular broad statement (in the application) supporting enablement, the Court states:

> Most often, additional factors, such as the teachings of pertinent references[*], will be available to substantiate any doubts that the asserted scope of enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. ***
>
> *Not necessarily *prior* art references, it should be noted, since the question would be regarding the *accuracy* of a statement in the specification, not whether that statement had been made before. [emphasis in the original]

In *In re Wilson* (135 USPQ 442, 444 (CCPA 1962)), the Court agreed that a reference, published after the filing date of the application, was properly cited to show a state of fact. In *In re Langer* (183 USPQ 288, 297 (CCPA 1974)) the Court again noted that later published references "are properly cited for the purpose of showing a fact." In *In re Rainer* (134 USPQ 343, 345 (CCPA 1962)) the Court found no error in the limited use made of a reference published after applicants' filing date to show a fact. While all of these cases involved publications cited by the Patent Office in support of rejections, as noted above, the same standard applies to evidence cited by applicants.

Applicants reiterate the fact that the above-mentioned references (Beattie et al., etc.) provide evidence showing successful use of combination promoters. For the same reasons discussed herein regarding Daly et al., 2001, these other references also support the specification. It is irrelevant for purposes of supporting that which the Applicants asserted to be true that the some of the references are after the filing date of the present application. Reconsideration of these references as evidence is requested.

A. Specification supports the claims

The specification provides sufficient support for the claimed hybrid promoters, specifically CMV/beta-actin fusions. As pointed out in the specification in the paragraph bridging pages 54 and 55,

> In certain embodiments the promoter can consist of fusions of one or more different types of promoters. For example, the regulatory regions of the CMV promoter and the beta actin promoter are well known and understood, examples, of which are disclosed herein. Parts of these promoters can be fused together to, for example, produce a CMV-beta actin fusion promoter, such as the one shown in SEQ ID NO:23. It is understood that this type of promoter has a CMV component and a beta actin component. These components can function independently as promoters, and thus, are themselves considered beta actin promoters and CMV promoters.

It is clearly stated that the promoter can consist of a combination of one or more different promoters. Thus, there is no question that the specification sufficiently describes hybrid promoters and that when reading the specification, one of skill in the art would understand what is meant by the hybrid promoter and understand the inventors to have been in possession of the same. Furthermore, the specification provides the necessary recombinant techniques to make these types of hybrid promoters, as well as providing the necessary information on how to use them, without undue experimentation. Nothing more is required.

Furthermore, the word promoter as used in the specification provides enough breadth for relying on Daly and Song. The Office Action alleges that the combination of the CMV enhancer/beta-actin promoter fusion is not the same as what is claimed (CMV promoter/beta-actin promoter). The Specification defines promoter as containing "core elements required for basic interaction of RNA polymerase and transcription factors, and may contain *upstream elements and response elements*. (emphasis added)" (paragraph bridging pages 46 and 47). To one skilled in the art, an enhancer would be commonly known as an upstream element and hence, would be considered part of the promoter in the context of the current application. On page 55 the specification states, "a promoter can be any portion of a known promoter that causes promoter activity." Enhancers, as stated in the specification, increase transcription and mediate

the regulation of transcription (second paragraph, page 53) which would undoubtedly be characterized as "promoter activity".

Thus, Daly et al., 2001 does teach "how to take regulatory regions of CMV and beta-actin and combine them to arrive at a functional, constitutive promoter." It is well known in the art that enhancers and promoters are both regulatory regions of DNA. Thus, Daly et al.'s hybrid CMV/beta-actin promoter teaches the combination of regulatory regions to produce a functional, constitutive promoter, providing support for the claimed compositions. (Likewise with Song et al.) In conclusion, the specification provides the necessary support for and enables the making and using of hybrid promoters generally, and specifically encompassing CMV and Beta Actin. Furthermore, the use of Daly et al. and Song et al., as well as the other references relied upon, provides appropriate evidence of the veracity of the Applicants statements. The written description and enablement rejections, as applied to the claimed fusion promoters, are traversed, and request for reconsideration and allowance is earnestly submitted.

Rejections Under 35 U.S.C. § 112, first paragraph related to GM Ganglioside and cell specific promoters

Claims 1, 4, 6, 16-18, 25, 26, 29, 30, 87, 89 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The Office Action maintains that the specification allegedly does not enable the skilled artisan to make and use the invention, a hybrid CMV/beta-actin promoter (discussed above), a product which cross corrects and catabolizes GM2, and which provides cell specific promoters.

The test of enablement under 35 U.S.C. § 112, first paragraph is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 USPQ 659 (CCPA 1976)(determining enablement is a question of law based on underlying factual findings); *In re Vaeck,* 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir.

1991); *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). The standard for enablement is set forth in *In re Wands*.

Claims 29 and 30 have been amended to depend from claim 27, rather than claim 26 to facilitate prosecution. Applicant reserves the right to prosecute the material at a later date. This moots the present rejection related to GM2 catabolizing activity.

Claim 89 has been canceled, without prejudice to facilitate prosecution. Applicant reserves the right to prosecute the material at a later date. This moots the present rejection related to SEQ ID NO:69.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 22 and 89 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 89 was rejected because it depended from canceled claim 88. Claim 89 has been canceled, which moots the present rejection.

Applicants have correctly amended claim 22 to depend from claim 20. Again, Applicants point out that this amendment is made merely to facilitate prosecution as a skilled artisan would know how to use hybrid promoters, as is discussed above.

Rejection Under 35 U.S.C. § 103

Claims 1-11, 13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, 135 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown and Mahuran (Am. J. of Hum Gen 53:497-508, 1993), in view of Li and Li (Int'l Congress Series 1223:3-15, 2001), Rossi et al. (Nat Gen 20:389-393, 1998), Kim et al. (Mol Cell Biol 12:3636-3643, 1992), Proia (PNAS 85:1883-1887, 1988), Myerowitz et al. (PNAS 82:7830-7834, 1985), Patapoutian et al. (WO 02/101045 A2), Hobbs (online, see office action for website), Hennighausen and Fleckenstein (EMBO J 5:1367-1371, 1986), Kost et al. (Nuc Acid Res 11:8287-8301, 1983), Kistner et al. (PNAS 93:10933-

10938, 1996), Sauer (Methods 14:381-392, 1998), Banerjee et al. (JBC 269:4819-4826, 1994). Applicants respectfully traverse this rejection.

The Office Action asserts that "an artisan would have combined Brown and Mahuran and Kim et al. in order to arrive at one expression system that expressed two transgenes of interest." Page 8, Office Action. This assertion is based on the conclusion by the Examiner that Brown and Mahuran teach "wild type and mutant forms of Hex-alpha and Hex-beta in separate plasmids. [and] Kim et al. teach that at the time of filing, that expression systems (i.e., vector) that expressed more than one transgene of interest were known." Page 8, Office Action. The Office Action also indicates that the teaching away of Guidottie et al. is not persuasive because there is no specific requirements to use the constructs in gene therapy, and one could simply use them in Cos cells as a measurement tool. In addition, the Office Action relies on a general assertion to dismiss the Applicant's previous evidence and argument in support of non-obviousness. This general assertion is that the claims are drawn to compounds and that the argument and evidence of teaching away provided are drawn to limitations that are not present in the claims.

It is true there are not limitations in the claims drawn to use as gene therapy. It is not correct, however, that the context and a reason for making the claimed molecules is not germane to the obviousness question, particularly for compounds and compositions whose specific utility is drawn to a pharmaceutical use. Specifically, the Office Action fails to state a *prima facie* case of obviousness, because of a failure to provide the appropriate motivation linked to the reasonable expectation of success required by the chemical case law, post *KSR*.

In support of this the Examiner is directed to *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Federal Circuit in *Takeda* found claims to compounds non-obvious over the close "lead compound" prior art, which differed by mere atoms, because the skilled artisan would not be led to modify the closest compound for the property, *the unclaimed property,* providing a specific utility for the compounds. The compounds were found to have the specific property of antidiabetic activity, which was not

recited in claim 1, a rejected claim. The art did not recognize this activity, and the court found that it would not be obvious because there was not a suggestion to start with the lead compound for the desired purpose, which is why a skilled artisan would modify the compound. If in the present circumstances, we assume the Office Action finds the two plasmid system of Brown and Mahuran the "closest compound," the question then becomes would one be motivated with a reasonable expectation of success to modify these "compounds" as disclosed in Brown and Mahuran to arrive at the claimed compound. The Office Action asserts that Kim et al., providing the missing element of a single plasmid having a linking sequence provides this motivation. Applicants have argued that Kim et al., does not provide the specific motivation and expectation necessary because of the specific requirements of GM2 catabolization, the specific utility for which the specification discusses these compounds in and the skilled artisan would desire to make them.

With respect to an expectation of success, the Office Action asserts that "There is a reasonable expectation of success that an artisan would have made the expression vector because Kim et a.. teach that the expression system express two or more transgenes spatially and temporally in one cell." Office Action at page 12. The Office Action misapplies the standard of a reasonable expectation of success. As elaborated on in *Takeda* and further set forth in *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1360 (Fed. Cir. 2007), *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.,* 533 F.3d 1353, 1357 (Fed. Cir. 2008), *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985), and *Proctor & Gamble Comp. v. Teva Pharmaceuticals USA Inc.*, Slip opinion 2008-1404, 1406, and 1408 (Fed. Cir. 2009)[5] in chemical cases, the reasonable

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[5] The Federal Circuit has held that a reasonable expectation of success should be present for a "composition" to be obvious under *KSR* and that the unpredictability of pharmaceutical compositions makes this a difficult hurdle to clear.

The Federal Circuit has found stated

> [To find a composition obvious a court must find that] . . .a person having ordinary skill in the art would have had "reason to attempt to make the

expectation of success is filtered through the predictability of the invention, which is defined by the claims. Thus, it is not obvious to arrive at the claimed compositions, having the limitation, "wherein the HEX-β and HEX-α can form a dimer, and wherein the dimer can catabolize GM2 ganglioside in vivo" just as in *Takeda* the claimed compound was not obvious for an *inferred* utility. Therefore, the Office Action fails to set forth a *prima facie* case of obviousness as required, and the Applicants traverse this rejection.

Nothwithstanding the lack of a *prima facie* case of obviousness, assuming the Office Actin has met this burden, the secondary consideration of teaching away by Guidotti rebuts this *prima facie* case. Because Brown and Mahuran, as well as Guidotti teach away from seeking this solution, it would be believed that the bicistronic construct of Kim et al., in combination with the Hex system of Brown and Mahuran would not yield *functioning*, *useful* molecules.

Additionally, as argued in the past, the claims require the limitation of "wherein the HEX-β and HEX-α can form a dimer, and wherein the dimer can catabolize GM2 ganglioside in vivo." The Office Action, gives no credence to this limitation. This very limitation specifically brings into play the purpose of making the claimed compositions, which specifically brings into play the teaching away of Guidotti et al., indicating this limitation is non functional (in vivo). As argued previously, Guidotti et al. teach that the construct of Brown and Mahuran does not form the functional dimer in vivo as required by the present claims. Therefore, assuming arguendo

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composition" known as risedronate and "a reasonable expectation of success in doing so.

PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007)." Furthermore, the Federal Circuit has indicated that to determine whether a composition which was a derivative was obvious a showing that the specific modifications would have been suggested is needed. (See *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008), *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007), and *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)). The Federal Circuit has also focused on unpredictability as an indicator of a lack of expectation of success. (See *Proctor & Gamble Comp. v. Teva Pharmaceuticals USA Inc.*, Slip opinion 2008-1404, 1406, and 1408 (Fed. Cir. 2009).

that the a *prima facie* case of obviousness has been made, Guidotti et al. provides secondary consideration evidence rebutting this *prima facie* case.

Lastly, as argued before, the claims are limited to a specific orientation, through the limitation of having GM2 catabolization in vivo because in a bicistronic vector there is a single orientation which achieves this limitation. It would not be obvious as asserted by the Office Action to arrive at the claimed compositions because at best the art relied on by the Examiner teaches a genus of bicistronic vectors, not the subset of bicistronic vectors that function as claimed.

Claim Objections

Should the base claims of claims 14, 138, and 142, ultimately be deemed unpatentable, claims 14, 138, and 142 will be rewritten in independent form.

Conclusion

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A deposit order account charge made electronically in the amount of $960.00, representing $555.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(3), $405.00 for the fee for a small entity under 37 C.F.R. § 1.17(e), Request for Continued Examination Transmittal and a Request for a Three Month Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-4667.

Respectfully submitted,

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